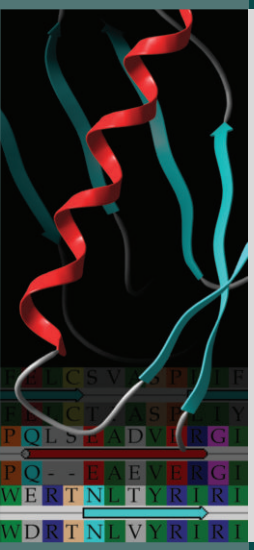


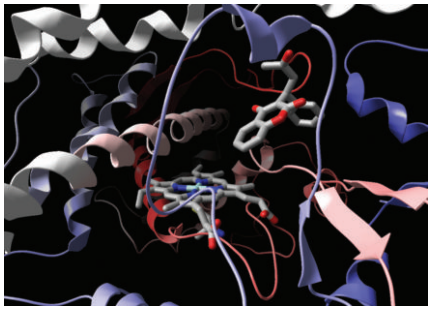
Prime

A powerful and innovative package for accurate protein structure predictions

Prime is a fully-integrated protein structure prediction program. It provides an easy-to-use interface that takes a novice user intuitively from sequence to alignment to refined structure. Prime also provides expert users complete control over calculational settings to maximize accuracy of predictions. Prime is a powerful and complete tool for generating accurate receptor models for structure-based drug design.

SCHRÖDINGER.

The Advantages of Accurate Receptor Models

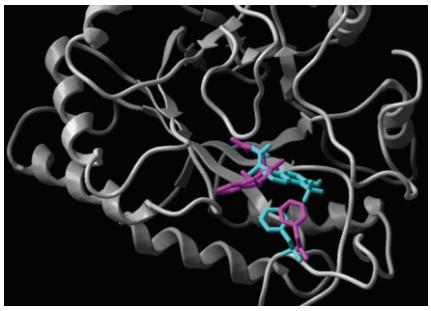


Homology model of human cytochrome P450 3A4 built on P450 2C9 (22% sequence identity). The heme and the docked substrate, (S)-warfarin, are shown in tubes.

Rational drug design has proven to be an effective and cost-saving approach to drug development. Lead discovery using virtual screening and lead optimization through detailed understanding of ligand-receptor interactions are now indispensable components of pharmaceutical research. An accurate model of the receptor, particularly of the active site, is central to all structure-based drug design efforts. While the recent explosion in genomic data has elucidated many protein sequences, there remain many pharmaceutically relevant targets for which no accurate 3D model exists.

An accurate protein structure prediction can not only provide a model where an experimental structure is unavailable, but can also refine experimental structures obtained through X-ray crystallography or NMR, providing an even more accurate and detailed starting point for subsequent simulations and computational analyses.

Prime: Maximizing Returns in Structure-Based Drug Design

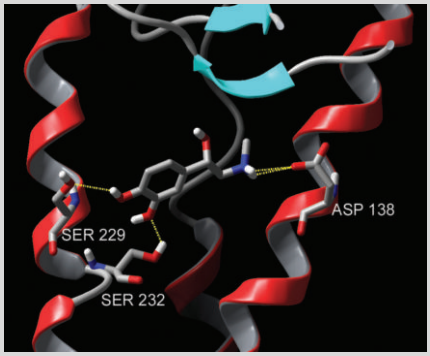


Two active binders (in cyan and magenta) are shown co-crystallized in the active site of aldose reductase. A phenylalanine residue of the receptor is shown to adopt very different conformations (in cyan and magenta, respectively) to accommodate the two ligands. Prime's Induced-fit modeling accurately predicts the change in a receptor's active site to optimize binding to different ligands.

Schrödinger's Prime is a fully-integrated protein structure prediction program specifically designed for structure-based drug design by providing:

- **Unmatched accuracy:** Prime combines improved science with new methods and algorithms to provide the highest accuracy in predicted structures.
- **Advanced simulation:** Prime's ligand-induced fit analysis refines active site geometries in the presence of ligands. Induced-fit modeling simulates flexibility of protein targets and identifies alternate binding modes of different ligand chemotypes.
- **Full integration:** Prime incorporates homology modeling and fold recognition into one package. Comparative modeling is used to generate accurate homology models for further structure-based studies. Threading and fold recognition techniques are used to create backbone models for early structural investigations or functional annotation in cases of low or no-sequence identity.
- **Easy-to-use interface:** Prime includes an intuitive step-by-step interface that takes a novice user through the workflow of structure prediction by supplying helpful default settings for each stage of the process. At the same time, Prime allows the expert user to specify and adjust parameters to optimize the quality of predictions. The Maestro interface provides additional structural and sequence visualization and analysis tools.
- **Cross-platform support:** Prime supports Linux and SGI. Calculations run across multiple CPUs can increase performance.

Performance-Driven Technology

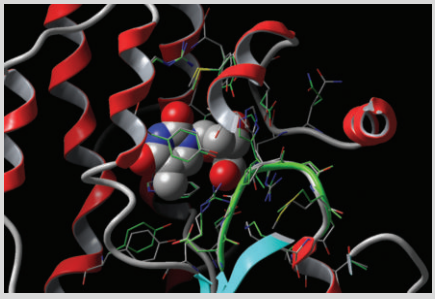


Homology model of beta-1 adrenergic receptor induced to fit epinephrine. The structure of the binding site for epinephrine is in good agreement with mutation experiments.

Prime incorporates the best available technologies:

- **State-of-the-art tools:** Prime provides powerful tools for template identification, alignment, model building, and refinement for the full range of sequence identity.
- **Innovative algorithms:** Prime uses new proprietary algorithms for sequence alignment in comparative modeling. Prime also makes novel use of composite templates and a global scoring function in threading.
- **Improved science:** Prime's all-atom force field and implicit solvent model have been specifically parameterized for modeling protein systems, and lead to superior accuracy in loop and side-chain predictions.
- **Advanced sampling:** Prime utilizes a hierarchical, multi-scale technique to exhaustively sample loop conformations. A clustering algorithm removes redundant candidate structures and efficiently reduces the number of loops for complete energy minimizations.
- **Complementary applications:** Together with Schrödinger's Glide application, Prime can address the issue of receptor flexibility in docking calculations. Using an induced-fit approach, Prime takes ligand-receptor complexes and produces accurate models of alternate active sites, which Glide can use in further screening calculations.

Loop and Side-Chain Predictions



Prime correctly predicted the conformation of a key active-site loop (residues 55-61) and the side chains of nearby residues of thymidine kinase (PDB ID: 1kim). The RMSD between the predicted (gray) and the native (green) loops is 0.65 Å.

The conformation of loops and side chains determine the structure of an active site, and an accurate model of the active site is critical to the success of any structure-based drug design project. Unfortunately, traditional homology modeling software packages exhibit the largest errors in non-conserved loop regions. Prime, through improved science and advanced sampling and refinement algorithms, achieves higher accuracy in loop predictions.

During one demonstration, a 7-residue loop (residues 55 to 61) was removed from the active site of thymidine kinase (1kim). Prime used extended loop sampling to predict the missing loop, as well as side chains of residues within 7.5 Å of the loop. The RMSD between the predicted and native loops was 0.65 Å. Similar successes have been observed for a wide range of systems:

- M. P. Jacobson, R. A. Friesner, Z. Xiang, and B. Honig. "On the Role of Crystal Packing Forces in Determining Protein Sidechain Conformations", *J. Mol. Bio.*, **2002**, *320*, 597-608.
- M. P. Jacobson, G. A. Kaminski, R. A. Friesner, and C. S. Rapp. "Force Field Validation Using Protein Sidechain Prediction", *J. Phys. Chem. B*, **2002**, *106*, 11673-11680.
- M. P. Jacobson, D. L. Pincus, C. S. Rapp, T. J. F. Day, B. Honig, D. E. Shaw, and R. A. Friesner. "A Hierarchical Approach to All-Atom Loop Prediction", *Proteins*, in press.

Evaluation Copies

To request an evaluation copy of Prime, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving Prime a thorough trial.

Prime

A powerful and innovative package for accurate protein structure predictions

System Requirements:

LINUX
- Pentium or better
- Linux kernel 2.4 (Red Hat 7.3) or later
- 512 MB memory

SGI
- R5000 or better
- IRIX 6.5.2m or later
- 512 MB memory

Additional Information:

www.schrodinger.com
info@schrodinger.com

A Coordinated Family of Products

Prime generates accurate receptor models that can be used in further studies such as virtual screening and ligand-receptor binding for lead discovery and optimization. Schrödinger's FirstDiscovery Suite is the ideal complement to Prime for structure-based analyses. The FirstDiscovery Suite includes three integrated modules:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Liaison:** Ligand-receptor binding free energies for lead optimization
- **QSite:** Mixed QM/MM for reactive chemistry at the enzyme active site

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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